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MINIREVIEW

Chemotactic Factors in Cerebrospinal Fluid during Bacterial Meningitis

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Bacterial meningitis is a devastating infectious disease, with a worldwide mortality rate of 20 to 30% despite antibiotic treatment (43, 45, 58). As many as 50% of survivors encounter neurological sequelae, such as hearing impairment, seizure disorders, and learning and behavioral problems (22, 32, 65).

In general, bacterial meningitis develops either when bacteria enter the systemic circulation and subsequently invade the central nervous system (CNS) or via continuous spread during a focal infection in the vicinity of the CNS (30, 57). The multiplication of bacteria in the CNS triggers a localized immune response, characterized by an influx of leukocytes. In a healthy state, the CNS is devoid of identifiable leukocytes (24, 91). However, in pathological conditions, leukocytes enter the brain in response to a variety of stimuli. Bacterial meningitis is characterized by pleocytosis of the cerebrospinal fluid (CSF), consisting predominantly of polymorphonuclear leukocytes (PMNs).

Leukocyte recruitment is a key aspect of the protective response against invading microorganisms, but over recent years, evidence has accumulated that leukocytes also contribute importantly to tissue damage in bacterial meningitis (30, 43, 46, 65, 85). Although leukocytes within the CSF are important for host defense, it has been demonstrated repeatedly that inhibition of leukocyte recruitment does not necessarily reduce bacterial clearance in the CNS (15, 51, 82). Altogether, leukocyte accumulation in CSF seems a useful target for additional therapeutic strategies.

Chemotaxis, directed migration of leukocyte subsets toward the CNS, is a complex process of which we have limited knowledge. First, leukocytes must adhere to endothelial cells, a process in which specific adhesion molecules (selectins) are involved, producing a rolling motion of leukocytes along the endothelium (81). Heparin interferes with this process and attenuates leukocyte rolling and sticking (89). In a secondary phase, mediated by integrins, leukocytes become strongly adherent, and once firmly attached, they can migrate between endothelial cell junctions (diapedesis) along a chemotactic gradient (60, 62, 80).

In 1975, Nolan et al. reported that CSF from patients with pneumococcal meningitis is chemotactic for granulocytes in vitro (47), a finding that was later confirmed by others (21, 35, 71, 95). Over recent decades, the chemotactic capacity of CSF of patients with bacterial meningitis has been further analyzed, and experimental models have provided more insight into the role of specific chemotactic factors in leukocyte trafficking during meningitis. In the present review, we summarize the available data on chemotactic factors that contribute to the development of pleocytosis during bacterial meningitis.

COMPLEMENT

Complement was first identified as a factor in serum that complemented antibodies in the killing of bacteria; we now know that complement is an important part of the innate immune system (87). The anaphylatoxins C3a and especially C5a are potent chemotaxins. The inflammatory functions of C3a and C5a are mediated via the specific C3a receptor and C5a receptor (CD88), respectively, which are expressed on a variety of cell types. Although the CNS is considered to be an immune-privileged organ, the brain represents a major site of complement synthesis (74). All classical- and alternative-pathway complement components can be synthesized in the CNS (6), and functional receptors for complement proteins are expressed by several cell types of the CNS (6, 20, 92). Local activation of the complement cascade has been demonstrated both in experimental meningitis (75) and in CSF from patients with bacterial meningitis (9, 16, 76, 90, 97). Normal CSF contains extremely low concentrations of C3 and C5, but during the course of meningitis, these complement components appear in CSF in parallel with the influx of leukocytes (16). Nolan et al. described the chemotactic activity of CSF from rabbits with experimental pneumococcal meningitis and speculated on the contribution of C5a to CSF chemotaxis, based on the molecular weight and heat stability of the chemotactic CSF (47). Subsequent studies identified the role of C5 in the accumulation of neutrophils in CSF during meningitis. Ernst et al. demonstrated chemotactic activity in CSF of rabbits, intrathecally challenged with *Streptococcus pneumoniae*, 2 h before PMNs began to accumulate (16). The chemotactic activity in CSF was significantly reduced by the addition of antibodies against C5, and preincubation of PMNs with rabbit C5a significantly diminished chemotactic responses of these cells to CSF from rabbits with pneumococcal meningitis, indicating a role for C5 in chemotaxis during experimental meningitis (16).

Two studies investigated the effect of in vivo inhibition of complement activation on the development of CSF leukocytosis during meningitis. In one study, in which rabbits with experimental pneumococcal meningitis were depleted of complement by cobra venom factor, the absence of complement was

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associated with a slight delay in the onset of CSF leukocytosis, but both the magnitude and the composition of the leukocytosis were unaltered (84).

CHEMOKINES

Chemokines, a subfamily of cytokines, are small (7- to 15-kDa) chemotactic proteins, which are classified into four families based on their structural differences in the number and spacing of conserved cysteine motifs in the NH_2 terminus (48, 60). Chemokines are divided into the CXC (or α) chemokine family, which comprises those members in which the first two cysteines are separated by an intervening amino acid, and the CC (or β) family, where they are adjacent. Two other subclasses have been identified, with one or two members in each to date. The C class has only two cysteines instead of four and has lymphotactin as its member, while the CX3C subclass has three amino acids between the first two cysteines and a mucin stalk at the N-terminal end and includes fractalkine. Not only are the groups structurally different; they also have different biological functions. In 1999, the constantly increasing number of chemokines led to a new nomenclature, according to that used for the classification of chemokine receptors (CXCL, CCL, CL, and CX_3CL, in which L stands for ligand). The CXC chemokines, the prototype of which is CXCL8 (interleukin-8 [IL-8]), show a specificity for the attraction and activation of PMNs, whereas the CC chemokines, such as CCL2 (monocyte chemotactic protein-1 [MCP-1]), CCL3 (macrophage inflammatory protein 1α [MIP-1α]), and CCL4 (MIP-1β), chemoattract monocytes, lymphocytes, eosinophils, and basophils. The CXC chemokines are further distinguished into two subgroups depending on the presence or absence of the Glu-Leu-Arg (ELR) motif which immediately precedes the first cysteine residue (ELR^+ CXC and ELR^- CXC chemokines, respectively). ELR^+ CXC chemokines have been shown to induce neutrophil chemotaxis and stimulate neutrophil activation in inflammatory responses. Several ELR^+ CXC chemokines exist in humans, including CXCL8 (IL-8), the growth-related oncogene family (GRO-α, -β, and -γ, also referred to as CXCL1 to CXCL3), and CXCL5 (epithelial-cell-derived neutrophil attractant 78 [ENA-78]). Rodent ELR^+ CXC chemokines have also been identified, among which MIP-2 and KC (61) are the most important.

CHEMOKINES IN THE CNS

Chemokines are constitutively expressed, and their expression can be increased by inflammatory mediators in a wide range of cell types and tissues, including the CNS (5). In many resident cells, such as microglial cells, astrocytes, and perivascular macrophages, chemokine production is rapidly upregulated upon activation by stimuli such as bacteria or inflammatory mediators (39, 56, 59). For instance, microglia (2, 14), astrocytes (2), and cerebral endothelial cells (25) are all capable of producing CXCL8. It has been demonstrated that the secretion of some chemokines, in particular CCL2 and CCL5 (regulated upon activation, normal T-cell expressed and secreted [RANTES]), by human meningeoma cells is dependent on the pathogen used to stimulate the cells (18). Chemokine secretion is typically induced by proinflammatory cytokines, such as IL-1 and tumor necrosis factor alpha (TNF-α) and bacterial products, such as lipopolysaccharide (LPS) (1, 4, 14). Chemokine activity may be regulated by inhibition of chemokine production by IL-4, IL-10, or transforming growth factor β (1, 14) or by neutralization of chemokine activity via the production of high-affinity antibodies to a specific chemokine (1). Chemokines mediate their action via cell surface receptors that are members of the rhodopsin superfamily of seven transmembrane-spanning G-protein-linked molecules. Five receptors for CXC chemokines have been identified in humans, CXC chemokine receptors 1 to 5 (CXCR1 to -5), whereas the CC family consists of nine receptors (CCR 1 to CCR 9). Downstream activation of mitogen-activated protein kinases, phosphoinositide 3-kinase, and small GTP-binding proteins such as RAC, RhoA, and CDC42H is presumably involved in the cytoskeletal reorganization and modulation of gene transcription necessary for cell migration (48, 63, 83). Modulation of the expression of chemokine receptors on the cell surface is another mechanism for control of chemokine activity (17, 36). Chemokines contribute to leukocyte recruitment by activating integrins and by promoting the migration of adherent leukocytes across the endothelium and through the extracellular matrix (10, 73). Furthermore, chemokines are able to activate leukocytes, enhancing phagocytosis, superoxide generation, and granule release (1, 4, 44).

CHEMOKINES IN CSF DURING BACTERIAL MENINGITIS

Considering the cellular composition of the inflammatory response to bacterial meningitis, ELR^+ CXC chemokines and, to a lesser extent, CC chemokines seem to play a role in the pathogenesis of the disease. Of the more than 40 chemokines identified, several have been demonstrated in CSF of patients with bacterial meningitis. In CSF from controls (without inflammatory CNS diseases), little if any CXCL8 is detectable. However, during both bacterial (23, 40–42, 50, 67, 68, 72, 86) and aseptic (27, 34, 40, 50, 72) meningitis, a significant upregulation of CXCL8 has been demonstrated. Some (23) but not all (72) studies reported increased serum CXCL8 levels in patients with bacterial meningitis. Contradictory results have been published on the presence or absence of a correlation between leukocyte counts in CSF and CXCL8 levels in CSF of patients with meningitis (40, 50, 71, 72). Østergaard et al. found that CSF CXCL8 levels correlated with CSF TNF-α levels, the CSF leukocyte count, protein levels, and the duration of hospitalization (50). In vitro, neutralizing antibodies against CXCL8 diminish the chemotactic activity of purulent CSF, and recombinant CXCL8 is able to exert chemotactic activity in CSF from controls (71, 103). Autoantibodies against CXCL8 seem to provide a mechanism to limit the bioavailability of free CXCL8 and to facilitate the clearance of CXCL8 by enhancing uptake by macrophages (33, 78). Elevated levels of anti-CXCL8 immunoglobulin G (IgG) and IgM were demonstrated in CSF from patients with purulent meningitis, but no correlation was found with anti-CXCL8 or CSF leukocyte counts (79).

Spanaus et al. measured CXCL8, CXCL1, CCL2, CCL3, CCL4, and CCL5 (RANTES) in CSF of patients with bacterial meningitis (71). All chemokines except CCL5 were detectable in most of the CSF samples from patients with bacterial men-

ingitis, whereas in control CSF samples, CXCL1, CCL3, and CCL4 levels were undetectable and CXCL8 and CCL2 were present in very low concentrations. In contrast with some data on in vitro chemokine production by human meningeoma cells upon stimulation with different pathogens (18), no differences in the expression of chemokines were found between various causative microorganisms. Possibly, the number of samples analyzed was too small to detect these differences. Moreover, the contributions of different cell types to chemokine production may equal these differences.

Furthermore, a strong correlation between levels of CXC chemokines and CC chemokines was demonstrated. Also, levels of CXCL8, CXCL1, CCL2, CCL3, and CCL4 correlated with the in vitro chemotactic activity of CSF for neutrophils or peripheral blood cells, and neutralizing antibodies against CXCL8, CXCL1, CCL2, and CCL3 significantly inhibited cell migration toward CSF from most patients with meningitis (34, 71). Strikingly, leukocyte counts from CSF did not correlate with chemokine concentrations or in vitro chemotactic activity. Thus, leukocyte migration in vivo is a more complex process in which other factors play a role as well.

Recently, we found CXCL5, a potent CXC chemokine, in CSF from most children with bacterial meningitis, exerting chemotactic activity on granulocytes (103). The chemotactic activity of CSF from patients with bacterial meningitis was significantly attenuated by neutralizing antibodies against CXCL5. Furthermore, CSF from controls exerted minor chemotactic activity, which could be strongly enhanced by the addition of recombinant CXCL5.

Upregulation of CCL2 in CSF during both bacterial and aseptic meningitis has been described repeatedly (71, 72) but correlated with CSF mononuclear cell counts in aseptic meningitis only (72). CCL3 was not detectable in one study (72), although others have reported significantly elevated levels in bacterial meningitis patients (26, 42, 71).

CHEMOKINES IN EXPERIMENTAL BACTERIAL MENINGITIS

Experimental models of bacterial meningitis are used to gain more insight into the mechanisms by which leukocytes are attracted toward the CNS. During experimental murine bacterial meningitis, we found increased concentrations of KC and MIP-2, the rodent counterparts of CXCL8, in mice with either pneumococcal or meningococcal meningitis (102) (P. J. G. Zwijnenburg, unpublished observation). Østergaard et al. found elevated levels of CXCL8 in CSF from rabbits with experimental pneumococcal meningitis, rising just before the influx of leukocytes (49). Furthermore, they demonstrated that after pretreatment with fucoidin, which inhibits leukocyte entry into the CSF, CXCL8 levels were elevated, indicating that resident immunocompetent cells, and not recruited leukocytes, are the major source of CXCL8 during meningitis (51). In an experimental model of *Listeria monocytogenes* meningitis, upregulation of CCL3, CCL4, and MIP-2 has been demonstrated (66).

Due to the presence of the blood-brain barrier, the function and action of chemokines in the CNS may differ from those in other organs. To gain insight in the local function of chemokines in the CNS, recombinant chemokines were administered into the brain or CSF in several studies. Bell et al. injected recombinant CXC chemokines (CXCL8, MIP-2, CXCL10 [IP-10]) and CC chemokines (CCL2 and CCL5) into the hippocampi of adult mice (7). CXCL8 injection was associated with PMN accumulation within 24 h after injection, mainly around the injection site, whereas intracranial MIP-2 injection induced a more pronounced and widespread leukocyte influx, consisting of PMNs and macrophages. CXCL10 did not provoke detectable leukocyte recruitment. The injection of CCL2 or CCL5 was followed by monocyte recruitment toward the brain parenchyma. None of these chemokines induced tissue damage or neuronal degeneration (7). Injection of MIP-1 into the CSF led to an early influx of PMNs, followed by mononuclear cells, and MIP-2 injection resulted in an influx of PMNs (64). To determine the interaction between KC and MIP-2, we injected these chemokines individually and together into the CSF of adult rats. MIP-2 was a more potent chemoattractant than KC, but the addition of KC to MIP-2 dramatically enhanced leukocyte recruitment toward the CSF, indicating synergy between these two chemokines (98). Surprisingly, intracisternal injection of rabbit or recombinant human CXCL8 into rabbits did not result in an elevation of the CSF leukocyte count within 8 h (13, 52). In accord with the experiments described by Bell et al. (7), it might be possible that leukocyte accumulation can only be found later (e.g., 24 h) after CXCL8 injection.

Furthermore, we investigated the roles of several cytokines in the pathogenesis of pneumococcal meningitis; these studies provide insight into the contributions of these cytokines to the development of leukocytosis of CSF. In IL-18 gene-deficient mice, lower levels of chemokines were present in the brain (99), suggesting that IL-18 has a stimulatory effect on the production of CXC chemokines. Furthermore, mice deficient in the gene encoding IL-1 receptor type I are unable to mount a strong release of KC and MIP-2 during meningitis; hence, an intact IL-1 signal is needed for chemokine production (100). In contrast, brain KC concentrations were significantly elevated in IL-10-deficient mice during meningitis, indicating that IL-10 diminishes the production of KC during meningitis, whereas MIP-2 levels were unaltered in the absence of IL-10 (101). Paul et al. induced pneumococcal meningitis in IL-6-deficient mice and found elevated CSF leukocyte counts and chemokine concentrations compared with those in infected wild-type mice (53). Similar results were obtained for rats with pneumococcal meningitis upon treatment with neutralizing anti-IL-6 antibodies, indicating a role for IL-6 in reducing CSF pleocytosis (53). These data indicate that the production of chemokines is regulated by a complex network of cytokines. Other inflammatory mediators are also involved in the regulation of chemokine production during meningitis. This has been demonstrated with mice deficient in the endothelial nitric oxide synthase gene, which display elevated levels of KC and MIP-2 and show enhanced pleocytosis of CSF during meningitis (29). In addition, experimental treatment with peroxynitrite scavengers results in lower concentrations of MIP-2 and decreases CSF leukocyte counts during meningitis (28).

Table 1 summarizes the available data on the involvement of chemokines in CSF pleocytosis during meningitis. The contribution of chemokines to leukocyte recruitment during meningitis might be a useful target for therapeutic intervention. Recently, modification of chemotaxis by treatment with neutralizing

TABLE 1. CXC and CC chemokines in CSF during bacterial meningitis and their demonstrated capacities to exert chemotaxis

Chemokine	CSF[a]	Chemotaxis[b]		Reference(s)
		In vivo	In vitro	
CXCL1 (GRO-α)	+		+	71, 103
CXCL5 (ENA-78)			+	103
CXCL8 (IL-8)	+	+/−	+	7, 13, 23, 40–42, 50, 52, 67, 71, 72, 86, 103
CCL2 (MCP-1)	+	+	+	7, 71, 72
CCL3 (MIP-1α)	+		+	26, 42, 71
CCL4 (MIP-1β)	+			71
CCL5 (RANTES)	−	+		7, 71

[a] Presence (+) or absence (−) of CXC and CC chemokines in CSF from patients with bacterial meningitis.
[b] Demonstrated capacity to exert chemotactic activity in vivo and in vitro.

antibodies against chemokines has been demonstrated in experimental models of bacterial meningitis. Intravenous treatment with antibodies against MIP-2 or CCL3 attenuated pleocytosis in an infant rat model of *Haemophilus influenzae* meningitis (12). Surprisingly, two independent reports on the effect of antibodies against CXCL8 on pleocytosis during meningitis have demonstrated that intravenous administration of anti-CXCL8 is much more potent at inhibiting leukocyte recruitment than intracisternal administration (13, 52). Both in LPS-induced meningitis (13) and in pneumococcal meningitis (52) in rabbits, intracisternal treatment with anti-CXCL8 moderately reduced pleocytosis, whereas intravenous treatment dramatically attenuated leukocyte accumulation, suggesting that the function of CXCL8 in chemotaxis is determined mainly by its interaction with the bloodstream side of endothelial cells of the blood-brain barrier.

RECENTLY IDENTIFIED CHEMOTACTIC FACTORS

Over recent years, the number of studies investigating the local inflammatory response during bacterial meningitis has been growing, and these studies have augmented our insight into the development of CSF pleocytosis. We now know that besides complement components and chemokines, other factors may exert chemotactic activity in CSF during meningitis.

Besides chemokines, other cytokines also exert chemoattractant properties. IL-16 has been reported to be chemoattractive (11), and recently, elevated levels of IL-16 have been demonstrated in CSF from patients with bacterial meningitis (77). Granulocyte colony-stimulating factor is another candidate for the generation of chemotactic activity, since its chemotactic capabilities (35, 88) and its presence in CSF from patients with viral (19, 69) and bacterial (70) meningitis, correlating with CSF leukocyte numbers, have been demonstrated.

Matrix metalloproteinase-9 (MMP-9) is a zinc-containing-endopeptidase that is involved in the degradation of the extracellular matrix during remodeling of connective tissue. MMP-9 is not constitutively expressed in CSF but occurs in pathological processes in the CNS (96), and elevated levels of MMP-9 have been demonstrated during bacterial meningitis (37, 38, 54, 68, 96). Several studies report a significant correlation between CSF MMP-9 levels and CSF leukocyte counts (3, 31, 96). It has been hypothesized that MMP-9 is involved in leukocyte migration by degrading the extracellular matrix, but MMP-9 also correlates with CSF chemotactic activity in a chemotaxis chamber, indicating that MMP-9 also exerts chemotactic activity directly (96). However, after injection of *S. pneumoniae* into the right forebrain, MMP-9 gene-deficient (MMP-$9^{-/-}$) mice have leukocyte counts in their CSF similar to those of wild-type mice (8). Thus, it remains unclear whether MMP-9 contributes directly to leukocyte migration toward the CNS or whether it reflects the presence or activity of leukocytes.

In recent years, numerous studies have demonstrated cross-links between the coagulation and fibrinolysis pathways and the innate immune response. Recently, it has been shown that the urokinase-type plasminogen activator (uPA)/uPA receptor (uPAR) system is involved in the pathogenesis of bacterial meningitis. Elevated levels of uPA and uPAR were found in CSF from patients with bacterial meningitis and correlated with CSF pleocytosis (94). Furthermore, in uPAR-deficient mice, CSF pleocytosis was significantly attenuated during experimental bacterial meningitis, despite the fact that levels of KC and MIP-2 were not affected (55). In contrast, CSF tissue-type plasminogen activator (tPA) levels are elevated during bacterial meningitis but do not correlate with CSF leukocyte counts (93). In line with these data, CSF pleocytosis during experimental bacterial meningitis did not differ between tPA-deficient and wild-type mice (55).

CONCLUSION

In recent years, considerable progress has been made in understanding the chemotaxis of leukocytes toward the CSF during bacterial meningitis, both in clinical and in experimental settings. As our understanding of chemotaxins grows, their role as mediators of leukocyte recruitment within a complex network becomes clearer. However, significant gaps in our knowledge remain and need to be addressed. In vitro and in vivo data are contradictory on specific issues. In addition, in vivo studies have shown that the chemotaxins identified so far explain chemotaxis only partly, suggesting that other factors play a role as well. Moreover, most of the data reviewed here are derived from experimental animal studies. The process of leukocyte attraction toward the CNS during bacterial meningitis is far more complicated.

Concerning the demonstrated dual role of leukocytes in host defense during bacterial meningitis, leukocyte accumulation in the CSF seems a useful target for additional therapeutic strategies. Experimental studies have provided evidence that specificity is a particular feature of chemokines and other chemotaxins, making this family attractive as therapeutic targets.

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